PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07C 255/29, 255/25, C07D 307/54, 231/12, 295/08, C07C 323/60, A61K 31/275, 31/33, A61P 19/00, C07D 333/24, 249/18

A1

(11) International Publication Number: WO 00/48992

(43) International Publication Date: 24 August 2000 (24.08.00)

(21) International Application Number: PCT/GB00/00539

(22) International Filing Date: 16 February 2000 (16.02.00)

(30) Priority Data:
9903861.4 20 February 1999 (20.02.99) GB

(71) Applicant *(for all designated States except US)*: ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

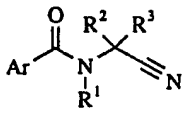
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: TUCKER, Howard [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). LARGE, Michael, Stewart [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). OLDFIELD, John [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). JOHNSTONE, Craig [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). EDWARDS, Philip, Neil [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: TIERNEY, Francis, John; AstraZeneca, Global Intellectual Property, P.O. Box 272, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4GR (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: ACYLATED AMINOACETONITRILES AS CYSTEINE PROTEASE INHIBITORS



(I)

(57) Abstract

A compound of formula (I): wherein R^1, R^2, R^3 and Ar are defined; a composition comprising a compound of formula (I) and a carrier or diluent; a compound of formula (I) for use as a medicament; the use of a compound of formula (I) in the manufacture of a medicament for use in the inhibition of a cysteine protease in a warm blooded animal; the use of a compound of formula (I) in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease in a warm blooded animal; and a method of treating a Cathepsin L or Cathepsin S mediated disease state in mammals which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

ACYLATED AMINOACETONITRILES AS CYSTEINE PROTEASE INHIBITORS

The present invention relates to compounds that are cysteine protease inhibitors and in particular compounds that are Cathepsin L inhibitors and or Cathepsin S inhibitors especially Cathepsin S inhibitors. The invention further relates to processes for their preparation, to intermediates useful in their preparation, to their use as therapeutic agents, to pharmaceutical compositions containing them and to a method of treating a Cathepsin L or Cathepsin S mediated disease state.

Cysteine proteases are enzymes important in normal cell physiology, but they are also associated with several disease states including inflammation, metastasis, tissue damage following myocardial infarction, bone resorption and muscle wasting in dystrophic diseases.

Cathepsins B, H, K, L, N and S are cysteinyl proteases involved in normal protein degradation and are normally located in the lysosomes of cells. However, when these enzymes are found outside the lysosomes they have been implicated as playing a causative role in a number of disease states including bone resorption disease such as osteoporosis.

The number of people living to an old age has increased dramatically in recent years. This has been marked by an increase in the number of people having osteoporosis and other diseases associated with old age. Osteoporosis is accompanied by a high incidence of bone fracture resulting in many aged patients being confined to their beds. There is therefore a great need for a pharmaceutical composition to treat or prevent this disease.

Living bone is continuously being remodelled and replenished by the process of resorption and deposition of the protein matrix and calcium minerals. These events are facilitated by the osteoclast, which has the ability to degrade and demineralise the bone, and the osteoblast which is responsible for new bone generation. In normal situations these processes are intimately linked resulting in little alteration of bone mass. However, pathological conditions exist in which there is an imbalance between their activities resulting in increased degradation and demineralisation of bone and the development of fragile and/or brittle bone structure, as seen during osteoporosis. While the exact mechanism for this resorption is not known, increased osteoclast activity, as realised by increased proteolytic activity, is a contributing factor, and selective inhibition of proteolytic action may result in the

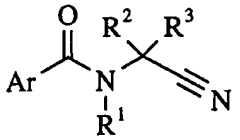
arrest or reversal of bone loss. The lysosomal cysteine proteinases, Cathepsins B, H, K, L, N and S have been postulated as the proteinases that are responsible for osteoclast bone resorption, because of their ability to degrade insoluble type I collagens at low pH.

Cathepsins B, H, K, L, N and S have been further implicated as playing a causative role in other diseases such as rheumatoid arthritis, osteoarthritis, tumour metastasis, pneumocystitis, Crithidia fusiculata, malaria, trypanosoma brucei brucei, schistosomiasis, periodontal disease, metachromatic leukodystrophy and muscular dystrophy. Cathepsins B, H, K, L, N and S, either alone or together, have also been implicated as playing a causative role in chronic obstructive pulmonary disease (COPD).

In recent years a number of synthetic inhibitors of cysteine proteases have been disclosed. US 5,055,451 discloses a series of peptidyl methyl ketones as thiol protease inhibitors; WO 95/15749 discloses peptidyl ketones with heterocyclic leaving groups as cysteine protease inhibitors; the *in vivo* inhibition of Cathepsin B by peptidyl (acyloxy) methyl ketones was discussed in *J. Med. Chem.* **1994**, *37*, 1833-40 and these types of compounds as inhibitors of cysteine protease inhibitors were also discussed in *J. Am. Chem. Soc.*, **1988**, *110*, 4429-4431; peptidyl diazomethyl ketones as specific inactivators of thiol proteinases was discussed in *J. Biol. Chem.*, **1981**, *256*, 4, 1923-8 and in *Methods in Enzymology*, **1981**, *80*, 820-5; the inhibiting activities of 1-peptidyl-2-haloacetyl hydrazines towards Cathepsin B and calpains was discussed in *Eur. J. Med. Chem.*, **1993**, 28 297-311 and peptidyl fluoromethyl ketones as inhibitors of Cathepsin B and the implication for treatment of Rheumatoid arthritis was discussed in *Biochemical Pharmacology*, **1992**, *44*, 6, 1201-7. Thus, there is a great need for a specific cysteine protease inhibitor, especially a Cathepsin L inhibitor or a Cathepsin S inhibitor.

The present invention discloses compounds with inhibitory activity of cysteine proteases and in particular of Cathepsin L and or Cathepsin S. The compounds of the invention are also useful in the treatment of chronic obstructive pulmonary disease (COPD).

Accordingly the present invention provides a compound of formula (**I**):



(I)

wherein

Ar is (optionally substituted phenylC_{1-6}alkyl)$_2$CH-, optionally substituted phenyl, optionally substituted naphthyl or an optionally substituted heteroaryl ring, said optional substituents being chosen from one or more of halo, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, C_{1-6}alkanoylamino, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, aminoC_{1-6}alkyl, *N*-(C_{1-6}alkyl)aminoC_{1-6}alkyl, (C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl, R^5S-, $R^5C(O)$- or R^5CH_2-; $\mathbf{R^5}$ is phenyl which is optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl or *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl;

$\mathbf{R^1}$ is H or C_{1-6}alkyl;

$\mathbf{R^2}$ is H, C_{1-6}alkyl (optionally substituted with one or more hydroxy, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, R^4, R^4C_{1-6}alkylsulphanyl, R^4C_{1-6}alkylsulphinyl or R^4C_{1-6}alkylsulphonyl), C_{1-6}alkoxy (optionally substituted with one or more halogen, C_{2-6}alkenyl, C_{2-6}alkynyl, R^4, R^4C_{2-6}alkenyl, R^4C_{2-6}alkynyl or Het), C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, R^4-, R^4S-, R^4C_{1-6}alkylsulphanyl, *N*-(R^4C_{1-6}alkyl)carbamoyl, *N*-(HetC_{1-6}alkyl)carbamoyl, C_{1-6}alkanoylamino, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl or C_{1-6}alkylsulphonyl; $\mathbf{R^4}$ is optionally substituted phenyl, or an optionally substituted 5 or 6 membered heteroaryl ring, said optional substituents on R^4 being chosen from one or more of C_{1-6}alkyl, halo,

trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-$(C_{1-6}alkyl)_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl or *N,N*-$(C_{1-6}alkyl)_2$sulphamoyl, wherein two such adjacent groups may join to form a 6-membered saturated, partially saturated or unsaturated ring;

Het is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms; and

$\mathbf{R^3}$ is H or C_{1-6}alkyl;

or a pharmaceutically acceptable salt thereof.

In this specification the term 'alkyl' includes straight chained and branched structures and ring systems. For example, C_{1-6}alkyl includes propyl, isopropyl, *t*-butyl, cyclopropyl and cyclohexyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only, references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only and references to individual cycloalkyl groups such as cyclohexyl are specific to the cyclic groups only.

A similar convention applies to other radicals, for example "aminoC_{1-6}alkyl" includes 1-aminoethyl and 2-aminoethyl.

The term "halo" refers to fluoro, chloro, bromo and iodo.

"Het" means, unless otherwise further specified, a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms. Examles of heteroatoms include nitrogen, oxygen and sulphur. Examples of "Het" include pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, triazole (especially 1,2,3-triazole), piperazinyl and morpholinyl. Examples of "Het" include pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl and morpholinyl.

"Heteroaryl ring " means, unless otherwise further specified, a monocyclic- or bicyclic-5-12 membered ring that contains some degree of unsaturation, with up to five ring heteroatoms selected from nitrogen, oxygen and sulphur. Examples of "heteroaryl ring" include thienyl, furyl, imidazolyl, thiazolyl, pyrimidinyl, pyridinyl, pyrrolyl, pyrazolyl, indolyl, benzimidazolyl, benzothiazolyl, quinolyl and isoquinolinyl. Examples of "5- or 6- membered

heteroaryl ring" include thienyl, furyl, imidazolyl, thiazolyl, pyrimidinyl, pyridinyl, pyrrolyl and pyrazolyl.

Examples of "C_{1-6}alkanoyloxy" are acetoxy and propionyloxy. Examples of "C_{1-6}alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_{1-6}alkoxy" include methoxy, ethoxy and propoxy. Examples of "C_{1-6}alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C_{1-6}alkylsulphanyl" include methylthio and ethylthio. Examples of "C_{1-6}alkylsulphinyl" include methylsulphinyl and ethylsulphinyl. Examples of "C_{1-6}alkylsulphonyl" include mesyl and ethylsulphonyl. Examples of "C_{1-6}alkanoyl" include acetyl and propionyl. Examples of "C_{1-6}alkylamino" include methylamino and ethylamino. Examples of "*N,N*-(C_{1-6}alkyl)$_2$amino" include *N,N*-dimethylamino, *N,N*-diethylamino and *N*-ethyl-*N*-methylamino. Examples of "C_{2-6}alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_{2-6}alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C_{1-6}alkyl)sulphamoyl" are *N*-methylsulphamoyl and *N*-ethylsulphamoyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$sulphamoyl" are *N,N*-dimethylsulphamoyl and *N,N*-diethylsulphamoyl. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" are *N,N*-dimethylaminocarbonyl and *N,N*-diethylaminocarbonyl. Examples of "*N*-(C_{1-6}alkyl)aminoC_{1-6}alkyl" are 2-*N*-methylaminoethyl and 3-*N*-ethylaminopropyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl" are 2-(*N,N*-dimethylamino)ethyl and 3-(*N,N*-diethylamino)propyl. Examples of "R^4C_{1-6}alkylsulphanyl" include R^4methylthio and 2-R^4ethylthio. Examples of "R^4C_{1-6}alkylsulphinyl" include R^4methylsulphinyl and 2-R^4ethylsulphinyl. Examples of "R^4C_{1-6}alkylsulphonyl" include R^4mesyl and 2-R^4ethylsulphonyl. Examples of R^4C_{2-6}alkenyl are R^4vinyl and R^4allyl. Examples of "C_{2-6}alkynyl" are R^4ethynyl and R^4propyn-1-yl. Examples of "*N*-(R^4C_{1-6}alkyl)carbamoyl" are *N*-(R^4methyl)aminocarbonyl and *N*-(2-R^4ethyl)aminocarbonyl. Examples of "*N*-(HetC_{1-6}alkyl)carbamoyl" are morpholinomethylaminocarbonyl and 2-(piperidinoethyl)aminocarbonyl.

Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups. For example

where optional substituents are chosen from one or more halo, C_{1-6}alkoxy and C_{1-6}alkyl, examples of possible combinations of substituents include 1) a bromo group, 2) two chloro groups, 3) a methoxy, ethoxy and propoxy substitutent, 4) a fluoro and a methoxy group, 5) a methoxy, a methyl and an ethyl group, and 6) a chloro, a methoxy and an ethyl group.

In one particular aspect the present invention provides a compound of formula (I) wherein **Ar** is (optionally substituted phenylC_{1-6}alkyl)$_2$CH-, optionally substituted phenyl, optionally substituted naphthyl or an optionally substituted heteroaryl ring, said optional substituents being chosen from one or more of halo, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, C_{1-6}alkanoylamino, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, aminoC_{1-6}alkyl, *N*-(C_{1-6}alkyl)aminoC_{1-6}alkyl, *N,N*-(C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl, R^5S-, $R^5C(O)$- and R^5CH_2- wherein $\mathbf{R^5}$ is phenyl which is optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl;

$\mathbf{R^1}$ is H or C_{1-6}alkyl;

$\mathbf{R^2}$ is H, C_{1-6}alkyl (optionally substituted with one or more hydroxy, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, R^4, R^4C_{1-6}alkylsulphanyl, R^4C_{1-6}alkylsulphinyl and R^4C_{1-6}alkylsulphonyl), or R^2 is C_{1-6}alkoxy (optionally substituted with one or more C_{2-6}alkenyl, C_{2-6}alkynyl, R^4, R^4C_{2-6}alkenyl, R^4C_{2-6}alkynyl and Het), or R^2 is C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, trifluoromethoxy, R^4-, R^4S-, R^4C_{1-6}alkylsulphanyl, *N*-(R^4C_{1-6}alkyl)carbamoyl, *N*-(HetC_{1-6}alkyl)carbamoyl, C_{1-6}alkanoylamino, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl or C_{1-6}alkylsulphonyl wherein $\mathbf{R^4}$ is optionally substituted phenyl, or an optionally substituted 5 or 6 membered heteroaryl ring said optional substituents on R^4 being

chosen from one or more of C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; and

R^3 is H or C_{1-6}alkyl;

or a pharmaceutically acceptable salt thereof.

In a still further aspect the present invention provides a compound of formula (I) wherein **Ar** is phenyl substituted with 1 to 3 chloro or methyl moieties, or naphthyl substituted with 1 bromo atom; **R**^{1} is H or C_{1-6}alkyl; **R**^{2} is H, C_{1-6}alkyl (optionally substituted with one or more hydroxy, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, R^4, R^4C_{1-6}alkylsulphanyl, R^4C_{1-6}alkylsulphinyl or R^4C_{1-6}alkylsulphonyl), C_{1-6}alkoxy (optionally substituted with one or more halogen, C_{2-6}alkenyl, C_{2-6}alkynyl, R^4, R^4C_{2-6}alkenyl, R^4C_{2-6}alkynyl or Het), C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, R^4-, R^4S-, R^4C_{1-6}alkylsulphanyl, *N*-(R^4C_{1-6}alkyl)carbamoyl, *N*-(HetC_{1-6}alkyl)carbamoyl, C_{1-6}alkanoylamino, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl or C_{1-6}alkylsulphonyl; **R**^{4} is optionally substituted phenyl, or an optionally substituted 5 or 6 membered heteroaryl ring, said optional substituents on R^4 being chosen from one or more of C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl or *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, wherein two such adjacent groups may join to form a 6-membered saturated, partially saturated or unsaturated ring; **Het** is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms; and, **R**^{3} is H or C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof; provided that when R^1, R^2 and R^3 are all hydrogen then Ar is not 4-chlorophenyl.

Preferred values for Ar, R^1, R^2 and R^3 are as follows.

Preferably Ar is optionally substituted phenyl or optionally substituted naphthyl said optional substituents being chosen from one or more of halo and C_{1-6}alkyl.

More preferably Ar is phenyl substituted with 1 to 3 chloro or methyl moieties, or naphthyl substituted with 1 bromo group.

Particularly Ar is phenyl substituted with 2 chloro groups or naphthyl substituted with 1 bromo group.

More particularly Ar is 2,6-dichlorophenyl or 1-bromo-napth-2-yl.

Preferably R^1 is hydrogen.

Preferably R^2 is hydrogen, C_{1-6}alkoxy (optionally substituted with one or more C_{2-6}alkynyl, R^4, R^4C_{2-6}alkenyl, R^4C_{2-6}alkynyl or Het), C_{1-6}alkanoylamino, trifluoromethoxy, C_{1-6}alkylsulphanyl or R^4 wherein R^4 is optionally substituted phenyl or an optionally substituted 5 or 6 membered heteroaryl ring said optional substituents being chosen from one or more C_{1-6}alkyl groups. Het is as defined above (that is it is: a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms; for example pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl or morpholinyl).

For example R^2 is hydrogen, C_{1-6} alkoxy (optionally substituted with one or more halogen, C_{2-6} alkynyl, R^4, R^4C_{2-6} alkenyl, R^4C_{2-6} alkynyl or Het), C_{1-6} alkanoylamino, C_{1-6} alkylsulphanyl or R^4; R^4 is optionally substituted phenyl or an optionally substituted 5 or 6 membered heteroaryl ring said optional substituents being chosen from one or more C_{1-6} alkyl groups, wherein two such adjacent groups may join to form a 6-membered saturated, partially saturated or unsaturated ring; Het is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms. For example R^4 is optionally substituted: phenyl, pyridyl, triazolyl, pyrazolyl, furyl or thienyl. For example Het is pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl or morpholinyl.

More preferably R^2 is hydrogen, methoxy, ethoxy, propoxy, 3-phenylprop-2-ynyloxy, 3-phenylprop-2-enyloxy, 2-morpholinoethoxy, acetamido, trifluoromethoxy, methylthio, ethylthio, propylthio, 2-propynyloxy, pyridylmethoxy, optionally substituted pyrazolyl, optionally substituted triazolyl, optionally substituted furyl, optionally substituted thienyl where said optional substituents are chosen from 1 or 2 methyl groups.

In another aspect the present invention provides a compound of formula (I) wherein R^2 is hydrogen, methoxy, ethoxy, propoxy, 3-phenylprop-2-ynyloxy, 3-phenylprop-2-enyloxy, 2-morpholinoethoxy, acetamido, 2,2,2-trifluoroethoxy, methylthio, ethylthio, *iso*-propylthio, 2-propynyloxy, pyridylmethoxy, optionally substituted pyrazolyl, optionally substituted triazolyl, optionally substituted furyl, optionally substituted thienyl where said optional substituents are chosen from 1 or 2 methyl groups or said 5-membered ring is fused to a benzene ring (to form, for example, a benzotriazolyl bicyclic ring system).

Particularly R^2 is methoxy, ethoxy, *n*-propoxy, 2-morpholinoethoxy, 2-propynyloxy and isopropylthio.

Preferably R^3 is hydrogen.

According to another aspect of the present invention there is provided a compound of the formula (I) wherein:

Ar is optionally substituted phenyl or optionally substituted naphthyl said optional substituents being chosen from one or more of halo and C_{1-6}alkyl;

R^1 is hydrogen;

R^2 is hydrogen, C_{1-6}alkoxy (optionally substituted with C_{2-6}alkynyl, R^4C_{2-6}alkenyl, R^4C_{2-6}alkynyl or Het), C_{1-6}alkanoylamino, trifluoromethoxy, C_{1-6}alkylsulphanyl or R^4 wherein R^4 is optionally substituted phenyl or an optionally substituted 5 or 6 membered heteroaryl ring said optional substituents being chosen from one or more C_{1-6}alkyl groups; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt thereof. Het is as defined above (that is it is: a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms; for example pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl or morpholinyl).

A further preferred class of compounds is that of formula (I) wherein:

Ar is phenyl substituted with 2 chloro groups or naphthyl substituted with 1 bromo group;

R^1 is hydrogen;

R^2 is methoxy, ethoxy, *n*-propoxy, 2-morpholinoethoxy, 2-propynyloxy or isopropylthio; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt thereof.

In a further aspect the present invention provides a compound of formula (I) wherein Ar is phenyl optionally substituted with halogen (such as chlorine) or C_{1-4} alkyl (such as methyl), or naphthyl optionally substituted by halogen (such as bromo); R^1 and R^3 are both hydrogen; and R^2 is hydrogen, C_{1-6} alkoxy (optionally substituted by halogen (such as fluorine), pyridinyl or morpholinyl), C_{1-6} alkylthio, C_{2-6} alkenyloxy (optionally substituted by phenyl), C_{2-6} alkynyloxy (optionally substituted by phenyl), C_{1-4} alkylcarbonylamino or optionally substituted 5 membered heteroaryl (such as thienyl, furyl (itself optionally substituted by C_{1-4} alkyl), pyrazolyl (itself optionally substituted by C_{1-4} alkyl) or benzotriazolyl); or a pharmaceutically acceptable salt thereof.

Preferred compounds are those of Examples 1 - 26 or a pharmaceutically acceptable salt thereof.

In a further aspect the present invention provides a compound of formula (I) wherein Ar is phenyl disubstituted with halogen (such as chlorine), or naphthyl monosubstituted by halogen (such as bromo); R^1 and R^3 are both hydrogen; and R^2 is C_{1-6} alkoxy (optionally substituted by morpholinyl), C_{1-6} alkylthio or C_{2-6} alkynyloxy; or a pharmaceutically acceptable salt. Thus, R^2 is, for example, methoxy, ethoxy, *n*-propoxy, *iso*-propylthio, 2-propynyloxy or 2-morpholinoethoxy.

Especially preferred compounds are those of Examples 1, 3, 5, 8, 10, 16 or 19 or a pharmaceutically acceptable salt thereof.

Suitable pharmaceutically acceptable salts include acid addition salts such as the methanesulphonate, fumarate, hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example a sodium salt, an alkaline earth metal salt for example a calcium or a magnesium salt, an organic amine salt for example a salt with triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N,N*-dibenzylethylamine or an amino acid for example a lysine salt. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically acceptable salt is a sodium salt.

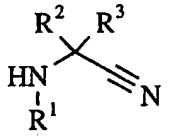
Some compounds of formula (I) may possess chiral centres. It is to be understood that the invention encompasses all such optical isomers and diasteroisomers of compounds of formula (I) which possess cysteine protease inhibitory activity.

The invention further relates to all tautomeric forms of the compounds of formula (I).

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms.

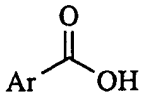
Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof. According to this aspect of the invention there is provided a process (in which variable groups are as defined for formula (I) unless otherwise stated) which comprises:

a) reacting an amine of formula (II)



(II)

with an acid of formula (III)



(III)

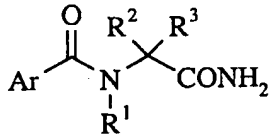
or a reactive derivative thereof.

A suitable reactive derivative of an acid of the formula (II) is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol, an ester such as pentafluorophenyl trifluoroacetate, an alcohol such as 1-hydroxybenzotriazole or a uronium salt such as 2-(1-benzotriazolyl)-1,1,3,3-

tetramethyluronium hexafluorophosphate(V); an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as *N,N*-dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

The reaction is preferably carried out in the presence of a suitable base such as, for example, an alkali or alkaline earth metal carbonate, alkoxide or hydroxide, for example sodium carbonate or potassium carbonate, or, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine or diazabicyclo-[5.4.0]undec-7-ene. The reaction is also preferably carried out in a suitable inert solvent or diluent, for example methylene chloride, acetonitrile, tetrahydrofuran, 1,2-dimethoxyethane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidin-2-one or dimethylsulphoxide, and at a temperature in the range, for example, -78° to 150°C, conveniently at or near ambient temperature.

b) dehydration of an amide of formula **(IV)**



(IV)

under standard conditions.

For example such a dehydration reaction may conventionally be carried out by reaction with a reagent such as trifluoroacetic anhydride. The reaction can conveniently be conducted in the presence of a suitable base as defined hereinbefore such as, for example, triethylamine. The reaction is also preferably carried out in a suitable inert solvent or diluent, as defined hereinbefore such as dichloromethane and at a temperature in the range, for example, -10°C to reflux conveniently 10°C to reflux.

If not commercially available, the necessary starting materials for the procedures described above may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally

similar compounds, by techniques which are analogous to the above described procedures or by techniques which are analogous to the procedures described in the examples.

For example, it will be appreciated that certain of the optional substituents on a phenyl or naphthyl or a heteroaryl ring in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and a Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an

aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

Many of the intermediates defined herein are novel, for example, those of the formula (IV) and these are provided as a further feature of the invention.

According to a further feature of the invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

According to a further feature of the present invention there is provided a method for producing inhibition of a cysteine protease in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of the formula wherein Ar is (optionally substituted phenylC_{1-6}alkyl)$_2$CH-, substituted phenyl (but not phenyl substituted only with nitro) or optionally substituted naphthyl, said optional substituents being chosen from one or more of halo, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, C_{1-6}alkanoylamino, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, aminoC_{1-6}alkyl, *N*-(C_{1-6}alkyl)aminoC_{1-6}alkyl, (C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl, R^5S-, R^5C(O)- or R^5CH_2-; R^5 is phenyl which is optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl or *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; R^1 is H or C_{1-6}alkyl; R^2 is H, C_{1-6}alkyl (optionally substituted with one or more hydroxy, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, R^4, R^4C_{1-6}alkylsulphanyl, R^4C_{1-6}alkylsulphinyl or R^4C_{1-6}alkylsulphonyl), C_{1-6}alkoxy (optionally substituted with one or more halogen, C_{2-6}alkenyl, C_{2-6}alkynyl, R^4, R^4C_{2-6}alkenyl, R^4C_{2-6}alkynyl or Het), C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, R^4-, R^4S-, R^4C_{1-6}alkylsulphanyl, *N*-(R^4C_{1-6}alkyl)carbamoyl, *N*-(HetC_{1-6}alkyl)carbamoyl, C_{1-6}alkanoylamino, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl or C_{1-6}alkylsulphonyl; R^4 is optionally substituted phenyl, or an optionally substituted 5 or 6 membered heteroaryl ring, said optional substituents on R^4 being chosen from one or more of C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl,

N-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl or *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, wherein two such adjacent groups may join to form a 6-membered saturated, partially saturated or unsaturated ring; Het is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms; and, R^3 is H or C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof; for use as a medicament.

In another aspect the present invention provides the use of a compound of the formula (I), wherein Ar is (optionally substituted phenylC_{1-6}alkyl)$_2$CH-, optionally substituted phenyl, optionally substituted naphthyl or an optionally substituted heteroaryl ring, said optional substituents being chosen from one or more of halo, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, C_{1-6}alkanoylamino, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, aminoC_{1-6}alkyl, *N*-(C_{1-6}alkyl)aminoC_{1-6}alkyl, (C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl, R^5S-, R^5C(O)- or R^5CH_2-; R^5 is phenyl which is optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl or *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; R^1 is H or C_{1-6}alkyl; R^2 is H, C_{1-6}alkyl (optionally substituted with one or more hydroxy, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, R^4, R^4C_{1-6}alkylsulphanyl, R^4C_{1-6}alkylsulphinyl or R^4C_{1-6}alkylsulphonyl), C_{1-6}alkoxy (optionally substituted with one or more halogen, C_{2-6}alkenyl, C_{2-6}alkynyl, R^4, R^4C_{2-6}alkenyl, R^4C_{2-6}alkynyl or Het), C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, R^4-, R^4S-, R^4C_{1-6}alkylsulphanyl, *N*-(R^4C_{1-6}alkyl)carbamoyl, *N*-(HetC_{1-6}alkyl)carbamoyl, C_{1-6}alkanoylamino, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl or C_{1-6}alkylsulphonyl; R^4 is optionally substituted phenyl, or an optionally substituted 5 or 6 membered heteroaryl ring,

said optional substituents on R^4 being chosen from one or more of C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-$(C_{1-6}alkyl)_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl or *N,N*-$(C_{1-6}alkyl)_2$sulphamoyl, wherein two such adjacent groups may join to form a 6-membered saturated, partially saturated or unsaturated ring; Het is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms; and, R^3 is H or C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof; in the manufacture of a medicament for use in the inhibition of a cysteine protease in a warm blooded animal, such as man.

The invention further provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease (COPD) in a warm blooded animal, such as man.

In particular the invention provides the use of a compound of the formula (I) of the present invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of Cathepsin S in a warm blooded animal, such as man.

The invention also provides the use of a compound of the formula (I) of the present invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of Cathepsin L in a warm blooded animal, such as man.

The present invention further provides a method of treating a Cathepsin L or Cathepsin S mediated disease state in mammals which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

In order to use a compound of the formula (I) or a pharmaceutically acceptable salt thereof for the therapeutic treatment of mammals including humans, in particular in the inhibition of a cysteine protease, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 100 mg and 1 g of the compound of this invention.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of 1 $mgkg^{-1}$ to 100 $mgkg^{-1}$ of the compound, preferably in the range of 5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), or a pharmaceutically-acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

(a)

Tablet I	mg/tablet
Compound X.	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.

(e)

Injection I	(50 mg/ml)
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

Inhibition of Cathepsin L and S.

The pharmaceutically-acceptable compounds of the present invention are useful in the inhibition of Cathepsin L and Cathepsin S, having a good activity *in vitro* against human Cathepsin L, human Cathepsin S and rabbit Cathepsin L.

Cathepsin L Assay

Recombinant human Cathepsin L was cloned and expressed in E Coli and purified using the method as described by Zeneca Limited, GB 2 306 961 A (published 14.05.1997).

Rabbit Cathepsin L was purified from rabbit liver as described by Maciewicz R. A. and Etherington D. J. (Biochem. J. (1988) 256, 433-440) except the liver homogenate supernatant

was concentrated by fractionation with $(NH_4)_2SO_4$ (20-80% saturation), and the pellet taken up and dialysed against 20mM NaAcetate pH 5.5, 1mM ethylenediaminetetraacetic acid (EDTA). The supernatant was then applied to a CM Sepharose ion exchange column and Cathepsin L eluted by gradient elution (0.25-0.75M NaCl). Fraction activity was determined using the synthetic substrate NCBz-Phe-Arg-NHMec as described. Cathepsin L fractions were pooled and desalted on a Sephacryl S100 column. Active fractions were pooled, adjusted to 20% saturation $(NH_4)_2SO_4$ and concentrated on a phenyl sepharose column. The remaining purification steps were as described.

Cathepsin L activity was measured based on the method of Barrett and Kirschke (1981 Methods in Enzymology, **80**, 535-561), using the fluorogenic substrates NCBz-Phe-Arg-NHMec. Inhibitors were identified by their ability to decrease the generation of the fluorescent leaving group (NHMec). Briefly the assay was as follows:

rHuman Cathepsin L or rabbit Cathepsin L (0.025 pmoles) was pre-incubated with or without test compound in 0.1M sodium acetate buffer pH4.5, 10mM cysteine, 0.1% Brij 35 at 25°C for 15 minutes in a solid black 96 well plate. Synthetic substrate, 20μM NCBz-Phe-Arg-NHMec, was added and the mixture incubated at 37°C for 30 minutes. The reaction was stopped by the addition of 0.1M sodium chloroacetate pH 4.3. Fluorescence was determined using a Fluoroskan II plate reader; excitation 355nm, emission 460nm. Compound potency was determined from the raw fluorescence data by calculating the IC_{50} against each enzyme using a PC graph drawing software package.

Cathepsin S assay.

Cloning and Expression of human Cathepsin S.

Recombinant human Cathepsin S was cloned and expressed in Baculovirus, by the following method. The cDNA sequence for human Cathepsin S is available in the EMBL database Accession Number M90696. This database sequence was used to prepare, by PCR on mRNA from human tissues, a recombinant plasmid carrying an insert with a DNA sequence identical to that of Cathepsin S in the EMBL database (Acc No M90696). The techniques for mRNA isolation, PCR and cloning are standard techniques known by those skilled in the art. Sequence determination of the recombinant insert was carried out using established DNA sequencing techniques.

The PCR was done so as to introduce an EcoRI cloning site 5' of the 'ATG' of Cathepsin S and an XbaI cloning site 3' of the 'Stop' codon. The PCR product was cloned between the EcoRI and XbaI sites of the baculovirus transfer vector pFASTBAC-1 (Bac-to-Bac Expression System commercially available from Gibco BRL –Life Technologies (cat no 10359-016)). This recombinant construct was used to generate, by standard techniques, a recombinant baculovirus capable of expressing preprocathepsin S.

Expression of recombinant Cathepsin S was tested for the baculoviral constructs by infection of two insect cell lines : Sf9 cells (ATCC No CRL-1711) and T.ni cells (Invitrogen, Cat No B855-02).

Purification of Cathepsin S

Method 1.

Procathepsin S was found in the insect cell medium and acid activated. The medium was mixed with an equal volume of 100mM Sodium Acetate buffer pH 4.5, 5mM dithiothreitol (DTT) and 5mM EDTA and incubated for one hour at 37°C method of Maubach et al (Eur. J. Biochem., 250, 745-750, 1997).

Method 2.

The pH of insect cell medium (10ml) containing procathepsin S was adjusted to 4.5 with glacial acetic acid and DTT and EDTA added to 5mM. The sample was then incubated at 37°C for 150min to enable conversion to the active enzyme. Ammonium sulphate was then added to 80% saturation and a pellet obtained by centrifugation. This pellet was redissolved in 2ml buffer A (100mM Tris, 500mM NaCl, 1mM EDTA, pH7.5) and mixed in a batchwise fashion with 100µl thiopropyl-Sepharose for 15min at 4°C. The non bound fraction was removed by a brief centrifugation and the gel washed with 2x1ml buffer A. Cathepsin S was then eluted by batch mixing with 0.4ml 20mM DTT in buffer A for 15min at 4°C.

Measurement of Cathepsin S Activity.

Cathepsin S activity was measured based on the method of Maubach et al (Eur. J. Biochem., 250, 745-750, 1997), using the fluorogenic substrate Z-Val-Val-Arg-NHMec.

Inhibitors were identified by their ability to decrease the generation of the fluorescent leaving group (NHMec). Briefly the assay was as follows:

rHuman Cathepsin S (1.5 nmoles) was pre-incubated with or without compounds in 50mM Potassium phosphate buffer pH 6.0-6.2, 20mM Na_2EDTA, 0.1% Brij at 25°C for 5 minutes in a solid black 96 well plate. Synthetic substrate, 20μM Z-Val-Val-Arg-NHMec, was added and the mixture incubated at 30°C for 20 minutes. The reaction was stopped by the addition of 0.1M sodium chloroacetate pH 4.3. Fluorescence was determined using a Fluoroskan II plate reader; excitation 355nm, emission 460nm. Compound potency was determined from the raw fluorescence data by calculating the IC_{50} against Cathepsin S using a PC graph drawing software package.

The following results were obtained on a standard *in-vitro* test system for the inhibition of Cathepsin L. The activity is described in terms of IC_{50}.

When tested in the above *in-vitro* tests the compounds of this invention give IC_{50}s in the range 1-10,000 nM.

The following data was obtained for Examples 5, 14 and 23.

Example	IC_{50} (Human)	IC_{50} (Rabbit)
5	1000	90
14	3113	-
23	38	38.27

Examples

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography

(TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra;

(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 250 MHz using perdeuterio dimethyl sulphoxide (DMSO-δ_6) as the solvent unless otherwise stated;

(viii) chemical symbols have their usual meanings; SI units and symbols are used;

(ix) solvent ratios are given in percentage by volume;

(x) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI) or fast atom bombardment (FAB); where values for m/z are given, generally only ions which indicate the parent mass are reported; and

(xi) melting points are uncorrected and (dec) indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations.

Example 1

2-(2,6-Dichlorobenzamido)-2-propoxyacetonitrile

Trifluoroacetic anhydride (0.51 ml) was added dropwise to a stirred mixture of 2-(2,6-dichlorobenzamido)-2-propoxyacetamide (360 mg) in pyridine (5 ml) at -10°C. The mixture was allowed to warm to ambient temperature then poured into ice-water and extracted with ether. The organic phase was washed with brine, dried and evaporated to dryness under reduced pressure. The residue was triturated with hexane and the insoluble solid collected to give 2-(2,6-dichlorobenzamido)-2-propoxyacetonitrile (235 mg). Mp 115-117°C; m/z 287 (MH^+); NMR 0.9 (t, 3H), 1.55 (m, 2H), 3.6 (t, 2H), 6.25 (d, 1H), 7.4-7.6 (m, 3H), 10.35 (d, 1H).

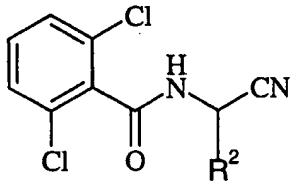
Example 2

2-(2,6-Dichlorobenzamido)-2-(3,5-dimethylpyrazol-1-yl)acetonitrile

$POCl_3$ (0.34 ml) was added dropwise to stirred ice cooled *N,N*-dimethylformamide (3 ml) and the mixture was added dropwise to a stirred solution of 2-(2,6-dichlorobenzamido)-2-(3,5-dimethylpyrazol-1-yl)acetamide (500 mg) in *N,N*-dimethylformamide (4 ml). The solution was stirred at ambient temperature for 0.5 hours then poured into water. The mixture was extracted with ethyl acetate and the extract was dried and evaporated to dryness. The residue was triturated with ether and the insoluble solid collected to give 2-(2,6-dichlorobenzamido)-2-(3,5-dimethylpyrazol-1-yl)acetonitrile (214 mg). m/z 323 (MH^+); NMR 2.15 (s, 3H), 2.35 (s, 3H), 5.95 (s, 1H), 7.4-7.55 (m, 4H), 10.7 (d, 1H).

Examples 3-15

The compounds listbed in the following table were made by processes analogous to either Example 1 or Example 2.



Example	R^2	mp (°C)	MH+	Example
3	ethoxy	151-152	273	1
4	pyrazol-1-yl	202-203	294 (M+)	1
5	methoxy	148-150	259	1
6	$PhC{\equiv}CCH_2O$-	165-167	359	1
7	$PhCH{=}CHCH_2O$-	137-139	361	1
8	2-Morpholinoethoxy	-	358	1
9	ethylthio	129-130	289	2
10	2-propynyloxy	82-87	283	1
11	methylthio	-	275	2
12	(2-pyridyl)methoxy	-	336	2
13	2,2,2-trifluoroethoxy	-	349 (MNa^+)	1

14	acetamido	-	286	2
15	benzotriazol-1-yl	-	346	2

Ph = phenyl

Example 16

2-(1-Bromo-2-naphthoylamino)-2-isopropylthioacetonitrile

The process described in Example 2 was repeated using 2-(1-bromo-2-naphthoylamino)-2-isopropylthioacetamide as starting material to give 2-(1-bromo-2-naphthoylamino)-2-isopropylthioacetonitrile. Mp 121-122°C; m/z 363 (MH^+) NMR ($CDCl_3$) 1.4 (d, 3H), 1.5 (d, 3H), 3.4 (m, 1H), 6.25 (d, 1H), 6.8 (m, 1H), 7.4 (d, 1H), 7.65 (m, 2H), 7.85 (m, 2H), 8.35 (d, 1H).

Example 17

2-(2,4-Dichlorobenzamido)-2-isopropylthioacetonitrile

The process described in Example 2 was repeated using 2-(2,4-dichlorobenzamido)-2-isopropylthioacetamide as starting material to give 2-(2,4-dichlorobenzamido)-2-isopropylthioacetonitrile. Mp 110-111°C; m/z 303 (MH^+) NMR ($CDCl_3$); 1.35 (d, 3H), 1.45 (d, 3H), 3.35 (m, 1H), 6.15 (d, 1H), 7.1 (m, 1H), 7.35 (dd, 1H), 7.45 (d, 1H), 7.7 (d, 1H).

Example 18

2-(2,6-Dichlorobenzamido)-2-isopropylthioacetonitrile

A solution of 2-benzyloxycarbonylamino-2-isopropylthioacetonitrile (450 mg) in dichloromethane (10 ml) was stirred under argon and then treated with iodotrimethylsilane (0.28 ml). The solution was stirred for 0.5 hours then treated with methanol (0.2 ml) and the mixture was evaporated to dryness under reduced pressure. A solution of the residue in dichloromethane (10 ml) was stirred under argon and treated with 2,6-dichlorobenzoyl chloride (420 mg) followed by triethylamine (0.5 ml) and the mixture was stirred at ambient temperature for 18 hours. The mixture was evaporated to dryness under reduced pressure and a solution of the residue in diethyl ether was washed successively with 1M hydrochloric acid, 1M sodium hydroxide and brine, dried and evaporated to dryness under reduced pressure. The residue was purified by flash chromatography using increasingly polar mixtures of dichloromethane and hexane as eluent followed by recrystallisation from carbon tetrachloride

to give 2-(2,6-dichlorobenzamido)-2-isopropylthioacetonitrile (67 mg). M/z 303 (MH^+); NMR ($CDCl_3$) 1.35 (d, 3H), 1.45 (d, 3H), 3.35 (m, 1H), 6.15 (d, 1H), 6.4 (m, 1H), 7.3-7.4 (m, 3H).

Example 19

2-(1-Bromo-2-naphthoylamino)-2-methoxyacetonitrile

N-bromosuccinimide (70 mg) was added to a stirred solution of 2-(1-bromo-2-naphthoylamino)-2-isopropylthioacetonitrile (120 mg) in methanol (2 ml) at -30°C. The solution was allowed to warm to ambient temperature. It was stirred for 2 hours then treated with water and the mixture was extracted with ethyl acetate. The mixture was washed with brine, dried and evaporated to dryness under reduced pressure and the residue recrystallised from a mixture of diethyl ether and hexane to give 2-(1-bromo-2-naphthoylamino)-2-methoxyacetonitrile (75 mg). Mp 162-164°C; m/z 319 (MH^+); NMR ($CDCl_3$) 3.65 (s, 3H), 6.2 (d, 1H), 6.95 (m, 1H), 7.5 (d, 1H), 7.65 (m, 2H), 7.9 (m, 2H), 8.4 (m, 1H).

Example 20

2-(2,4-Dichlorobenzamido)-2-methoxyacetonitrile

The process described in Example 19 was repeated using 2-(2,4-dichlorobenzamido)-2-isopropylthioacetonitrile as starting material to give 2-(2,4-dichlorobenzamido)-2-methoxyacetonitrile. Mp 105-106°C; m/z 259 (MH^+); NMR ($CDCl_3$) 3.55 (s, 3H), 6.15 (d, 1H), 7.2 (m, 1H), 7.4 (dd, 1H), 7.5 (d, 1H), 7.7 (d, 1H).

Example 21

2-(1-Bromo-2-naphthoylamino)acetonitrile

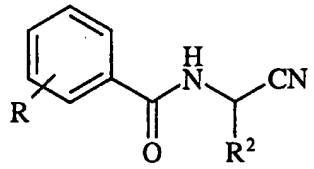
N,N-Dimethylformamide (0.05 ml) was added to a stirred mixture of 1-bromo-2-naphthoic acid (2 g) , dichloromethane (20 ml) and oxalyl chloride ((0.9 ml) and the mixture was stirred for 1 hour then evaporated to dryness under reduced pressure.

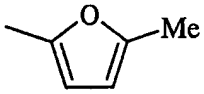
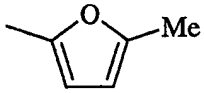
A portion of the acid chloride (270 mg) was added to a stirred, ice cooled mixture of aminoacetonitrile hydrochloride (0.14 g),dichloromethane (20 ml) and triethylamine (0.5 ml) The mixture was stirred at ambient temperature for 18 hours. Water was added and the dichoromethane separated and washed successively with 1M hydrochloric acid, 1M sodium hydroxide and brine, dried and evaporated to dryness under reduced pressure. The residue was recrystallised from a mixture of ethyl acetate and hexane to give 2-(1-bromo-2-

naphthoylamino)acetonitrile. Mp 172-173°C; m/z 289 (MH^+); NMR ($CDCl_3$) 4.45 (d, 2H), 6.65 (m, 1H), 7.5 (d, 1H), 7.65 (m, 2H), 7.85 (m, 2H), 8.35 (m, 1H).

Example 22 - 25

The following analogues were prepared according to the method of Example 21 using the appropriate benzoic acids and substituted aminoacetonitriles:



Example	R	R^2	Mp °C
22	2,4-diCl	2-furyl	169-170
23	2,4,6-triMe		115.5-118
24	2-Cl		72.5-74
25	2,6-diCl	2-furyl	131-132

Example 26

2-(1-Bromo-2-naphthoylamino)-2-(2-thienyl)acetonitrile

The process described in Example 21 was repeated using 2-(2-thienyl)-2-aminoacetonitrile instead of aminoacetonitrile to give 2-(1-bromo-2-naphthoylamino)-2-(2-thienyl)acetonitrile. Mp 162-163°C; m/z 371 (M^+); NMR ($CDCl_3$); 6.55 (d, 2H), 6.7 (m, 1H), 7.1 (m, 1H), 7.4 (m, 2H), 7.5 (d, 1H), 7.65 (m, 2H), 7.85 (m, 2H), 8.35 (m, 1H).

Preparation of Starting Materials

The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions (Methods A-F) are illustrations but not limitations of the preparation of some of the starting materials used in the above reactions.

Method A

2-(2-Furyl)aminoacetonitrile

Ammonium chloride (25 g) was added to a solution of 2-furfuraldehyde (25 g) in diethyl ether (250 ml). A solution of sodium cyanide (17 g) in water (80 ml) was added over 20 minutes. The reaction mixture was stirred at ambient temperature for 14 hours , the aqueous layer was removed and the organic layer was washed twice with saturated aqueous sodium hydrogen carbonate solution (100 ml each time), dried and evaporated to dryness. The residue was dissolved in diethyl ether (250 ml) and cooled to 0 °C. Hydrogen chloride gas was bubbled through the solution keeping the temperature below 10 °C. 2-(2-Furyl)aminoacetonitrile hydrochloride was filtered and dried, yield 33 g. ^{1}H NMR 6.19 (s, 1H), 6.56 (m, 1H), 6.78 (d, 1H), 7.83 (m, 1H), 9.83 (broad s, 2H).

Methods A1-3

Following the method outlined in Method A and using the appropriate aldehyde there was prepared:

A1 2-[2-(5-methylfuryl)]aminoacetonitrile hydrochloride;

A2 2-(3-furyl)aminoacetonitrile hydrochloride;

A3 2-(2-thienyl)aminoacetonitrile hydrochloride;

Method B

2-(2,6-Dichlorobenzamido)-2-propoxyacetamide

A solution of 2,6-dichlorobenzoyl chloride (5 ml) in dichloromethane (5 ml) was added dropwise to a stirred mixture of aminoacetonitrile hydrogen sulphate (5.38 g), dichloromethane (75 ml) and triethylamine (17.5 ml) keeping the temperature below 30°C. The mixture was stirred at ambient temperature for 16 hours then washed successively with water and brine, dried and evaporated to dryness under reduced pressure. The residue was purified by flash chromatography using 1% methanol in dichloromethane as eluent to give 2-(2,6-dichlorobenzamido)acetonitrile (6.26 g). Mp 130-134°C; m/z 229 (MH^+).

A mixture of 2-(2,6-dichlorobenzamido)acetonitrile (2 g), glacial acetic acid (15 ml) and bromine (0.45 ml) was stirred in a bath at 50°C until the solution had decolourised. The mixture was cooled and the insoluble solid collected and washed with dichloromethane to give

2-(2,6-dichlorobenzamido)-2-bromoacetamide (1.43 g), which was used without further purification.

A mixture of 2-(2,6-dichlorobenzamido)-2-bromoacetamide (700 mg) and *n*-propanol (4 ml) was heated at 90°C for 5 min and then evaporated to dryness under reduced pressure. The residue was partitioned between chloroform and aqueous sodium hydrogen carbonate, and the organic phase was dried and evaporated to dryness under reduced pressure to give 2-(2,6-dichlorobenzamido)-2-propoxyacetamide (370 mg). M/z 287 (MH^+) which was used without further purification.

Methods B 1-2

Using a process similar to that described in Method C using the appropriate alcohol there was prepared:

B1 2-(2,6-dichlorobenzamido)-2-ethoxyacetamide. M/z 291 (MH^+);

B2 2-(2,6-dichlorobenzamido)-2-methoxyacetamide. M/z 277 (MH^+).

Methods B 3-10

By a process similar to that described in preparation of the intermediate for Method C but using tetrahydrofuran as solvent instead of excess alcohol there was prepared:

2-(2,6-dichlorobenzamido)-2-(3-phenylprop-2-ynyloxy)acetamide. M/z 377 (MH^+);

2-(2,6-dichlorobenzamido)-2-(3-phenylprop-2-enyloxy)acetamide. M/z 379 (MH^+);

2-(2,6-dichlorobenzamido)-2-(2-morpholinoethoxy)acetamide. M/z 376 (MH^+);

2-(2,6-dichlorobenzamido)-2-ethylthioacetamide. M/z 307 (MH^+);

2-(2,6-dichlorobenzamido)-2-(2-propynyl)oxyacetamide. M/z 300 (M^+);

2-(2,6-dichlorobenzamido)-2-methylthioacetamide. M/z 293 (MH^+);

2-(2,6-dichlorobenzamido)-2-[(2-pyridyl)methoxy]acetamide. M/z 354 (MH^+);

2-(2,6-dichlorobenzamido)-2-(2,2,2-trifluoroethoxy)acetamide. M/z 345 (MH^+).

Method C

2-(2,6-Dichlorobenzamido)-2-(3,5-dimethylpyrazol-1-yl)acetamide

A mixture of 2-(2,6-dichlorobenzamido)-2-bromoacetamide (500 mg), pyridine (4 ml) and 3,5-dimethylpyrazole (442 mg) was heated at 90°C for 5 min and then cooled and diluted to 60 ml with water. The mixture was extracted with ethyl acetate and the organic phase was washed with water, dried and evaporated to dryness under reduced pressure. The residue was

triturated with ether and the insoluble solid collected to give 2-(2,6-dichlorobenzamido)-2-(3,5-dimethylpyrazol-1-yl)acetamide (227 mg). M/z 341 (MH^+).

Method C1

Using a process similar to that described in Method C using pyrazole instead of 3,5-dimethylpyrazole there was prepared:

C1 2-(2,6-dichlorobenzamido)-2-(pyrazol-1-yl)acetamide M/z 313 (MH^+).

Method D

2-Benzotriazol-1-yl-2-(2,6-dichlorobenzamido)acetamide

A mixture of 2,6-dichlorobenzamide (3 g), ethyl glyoxalate (4 g), benzotriazole (2.8 g), para-toluenesulphonic acid (0.2 g) and toluene (100 ml) was heated at reflux in a flask fitted with a Dean and Stark trap for 5 hours. The mixture was evaporated to dryness under reduced pressure and the residue purified by medium pressure liquid chromatography using 0.5 - 1% methanol in dichloromethane as eluent to give ethyl 2-benzotriazol-1-yl-2-(2,6-dichlorobenzamido)acetate (1.18 g). Mp 194-195°C; m/z 393 (MH^+).

A mixture of ethyl 2-benzotriazol-1-yl-2-(2,6-dichlorobenzamido)acetate (350 mg) and a saturated solution of ammonia in ethanol (8 ml) was stirred at 0°C for 0.5 hours then kept at 4°C for 18 hours. The solid which had precipitated was collected to give 2-benzotriazol-1-yl-2-(2,6-dichlorobenzamido)acetamide (55 mg). M/z 364 (MH^+).

Method E

2-Acetamido-2-(2,6-dichlorobenzamido)acetamide

The filtrate from the above experiment was evaporated to dryness under reduced pressure and the residue was dissolved in a saturated solution of ammonia in ethanol (8 ml) and the solution was kept at ambient temperature for 60 hours. The solution was evaporated to dryness under reduced pressure, the residue was triturated with ether and the insoluble solid collected to give 2-amino-2-(2,6-dichlorobenzamido)acetamide (148 mg).

A mixture of 2-amino-2-(2,6-dichlorobenzamido)acetamide (120 mg), *N,N*-dimethylformamide (2 ml) and pentafluorophenylacetate (310 mg) was stirred at ambient temperature for 1 hour. The mixture was treated with water and ethyl acetate and the insoluble solid collected to give 2-acetamido-2-(2,6-dichlorobenzamido)acetamide (87 mg). M/z 304 (MH^+).

Method F

2-(1-Bromo-2-naphthoylamino)-2-isopropylthioacetamide

A mixture of 1-bromo-2-naphthoic acid (1.75 g), dichloromethane (20 ml) and oxalyl chloride (0.9 ml) was stirred while adding *N,N*-dimethylformamide (0.05 ml), the mixture was stirred a further 1 hour and then evaporated to dryness. The residual acid chloride was stirred with concentrated aqueous ammonia at for 1 hour and the insoluble solid was collected and washed with water to give 1-bromo-2-naphthoylamide (1.67 g),which was used without further purification.

A mixture of 1-bromo-2-naphthoylamide (750 mg), glyoxilic acid monohydrate (304 mg) and acetone (5 ml) was stirred at reflux for 3 hours and the resulting solution was evaporated to dryness under reduced pressure. A mixture of the residue, isopropanethiol (0.38 g), dichloroethane (10 ml) and 2-naphthalenesulphonic acid (30 mg) was stirred at reflux for 4 hours and the resulting solution was evaporated to dryness under reduced pressure. A mixture of the residue, methanol (30 ml) and concentrated sulphuric acid (2 ml) was stirred at ambient temperature for 2 hours.The solution was poured into a stirred mixture of ice and saturated sodium bicarbonate solution and the mixture was extracted with diethyl ether.The extracts were washed with brine, dried and evaporated to dryness under reduced pressure and the residue was purified by flash chromatography using increasingly polar mixtures of ethylacetate and hexane as eluent to give ethyl 2-(1-bromo-2-naphthoylamino)-2-isopropylthioacetate (550 mg). M/z 396 (MH^+).

A mixture of ethyl 2-(1-bromo-2-naphthoylamino)-2-isopropylthioacetate (520 mg), methanol (10 ml) and concentrated aqueous ammonia was stirred at ambient temperature for 3 hours. The solution was diluted with water and the precipitate collected to give 2-(1-bromo-2-naphthoylamino)-2-isopropylthioacetamide (450 mg). Mp 119-120°C; m/z 381 (MH^+).

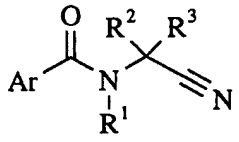
Method F1

By a procedure analogous to the procedure described in Method F and using the appropriate starting materials, there was prepared:

F1: 2-(2,4-dichlorobenzamido)-2-isopropylthioacetamide. M/z 321 (MH^+).

CLAIMS

1. A compound of formula (I):

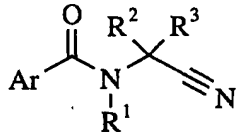


(I)

wherein **Ar** is (optionally substituted phenylC_{1-6}alkyl)$_2$CH-, optionally substituted phenyl, optionally substituted naphthyl or an optionally substituted heteroaryl ring, said optional substituents being chosen from one or more of halo, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, C_{1-6}alkanoylamino, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, aminoC_{1-6}alkyl, *N*-(C_{1-6}alkyl)aminoC_{1-6}alkyl, (C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl, R^5S-, R^5C(O)- or R^5CH_2-; $\mathbf{R^5}$ is phenyl which is optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl or *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; $\mathbf{R^1}$ is H or C_{1-6}alkyl; $\mathbf{R^2}$ is H, C_{1-6}alkyl (optionally substituted with one or more hydroxy, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, R^4, R^4C_{1-6}alkylsulphanyl, R^4C_{1-6}alkylsulphinyl or R^4C_{1-6}alkylsulphonyl), C_{1-6}alkoxy (optionally substituted with one or more halogen, C_{2-6}alkenyl, C_{2-6}alkynyl, R^4, R^4C_{2-6}alkenyl, R^4C_{2-6}alkynyl or Het), C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, R^4-, R^4S-, R^4C_{1-6}alkylsulphanyl, *N*-(R^4C_{1-6}alkyl)carbamoyl, *N*-(HetC_{1-6}alkyl)carbamoyl, C_{1-6}alkanoylamino, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl

or C_{1-6}alkylsulphonyl; $\mathbf{R^4}$ is optionally substituted phenyl, or an optionally substituted 5 or 6 membered heteroaryl ring, said optional substituents on R^4 being chosen from one or more of C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-$(C_{1-6}alkyl)_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl or *N,N*-$(C_{1-6}alkyl)_2$sulphamoyl, wherein two such adjacent groups may join to form a 6-membered saturated, partially saturated or unsaturated ring; **Het** is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms; and, $\mathbf{R^3}$ is H or C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof.

2. A compound of formula (**I**):



(**I**)

wherein **Ar** is phenyl substituted with 1 to 3 chloro or methyl moieties, or naphthyl substituted with 1 bromo atom; $\mathbf{R^1}$ is H or C_{1-6}alkyl; $\mathbf{R^2}$ is H, C_{1-6}alkyl (optionally substituted with one or more hydroxy, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, R^4, R^4C_{1-6}alkylsulphanyl, R^4C_{1-6}alkylsulphinyl or R^4C_{1-6}alkylsulphonyl), C_{1-6}alkoxy (optionally substituted with one or more halogen, C_{2-6}alkenyl, C_{2-6}alkynyl, R^4, R^4C_{2-6}alkenyl, R^4C_{2-6}alkynyl or Het), C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-$(C_{1-6}alkyl)_2$carbamoyl, R^4-, R^4S-, R^4C_{1-6}alkylsulphanyl, *N*-(R^4C_{1-6}alkyl)carbamoyl, *N*-($HetC_{1-6}$alkyl)carbamoyl, C_{1-6}alkanoylamino, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl or C_{1-6}alkylsulphonyl; $\mathbf{R^4}$ is optionally substituted phenyl, or an optionally substituted 5 or 6 membered heteroaryl ring, said optional substituents on R^4 being chosen from one or more of C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino,

C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl or *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, wherein two such adjacent groups may join to form a 6-membered saturated, partially saturated or unsaturated ring; **Het** is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms; and, $\mathbf{R^3}$ is H or C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof; provided that when R^1, R^2 and R^3 are all hydrogen then Ar is not 4-chlorophenyl.

3. A compound as claimed in claim 2 wherein R^1 is hydrogen.

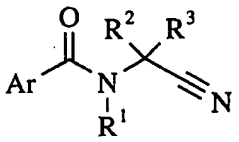
4. A compound as claimed in claim 2 or 3 wherein R^3 is hydrogen.

5. A compound as claimed in claim 2, 3 or 4 wherein R^2 is hydrogen, C_{1-6} alkoxy (optionally substituted with one or more halogen, C_{2-6} alkynyl, R^4, R^4C_{2-6} alkenyl, R^4C_{2-6} alkynyl or Het), C_{1-6} alkanoylamino, C_{1-6} alkylsulphanyl or R^4; R^4 is optionally substituted phenyl or an optionally substituted 5 or 6 membered heteroaryl ring said optional substituents being chosen from one or more C_{1-6} alkyl groups, wherein two such adjacent groups may join to form a 6-membered saturated, partially saturated or unsaturated ring; Het is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms.

6. A compound as claimed in any one of claims 2 to 5 wherein R^2 is hydrogen, methoxy, ethoxy, propoxy, 3-phenylprop-2-ynyloxy, 3-phenylprop-2-enyloxy, 2-morpholinoethoxy, acetamido, 2,2,2-trifluoroethoxy, methylthio, ethylthio, *iso*-propylthio, 2-propynyloxy, pyridylmethoxy, optionally substituted pyrazolyl, optionally substituted triazolyl, optionally substituted furyl, optionally substituted thienyl where said optional substituents are chosen from 1 or 2 methyl groups or said 5-membered ring is fused to a benzene ring (to form, for example, a benzotriazolyl bicyclic ring system).

7. A pharmaceutical composition comprising a compound of formula (I) as claimed in claim 1 or 2 and a pharmaceutically acceptable diluent or carrier.

8. A compound of formula (I):



(I)

wherein **Ar** is (optionally substituted phenylC_{1-6}alkyl)$_2$CH-, substituted phenyl (but not phenyl substituted only with nitro) or optionally substituted naphthyl, said optional substituents being chosen from one or more of halo, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, C_{1-6}alkanoylamino, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, aminoC_{1-6}alkyl, *N*-(C_{1-6}alkyl)aminoC_{1-6}alkyl, (C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl, R^5S-, R^5C(O)- or R^5CH_2-; $\mathbf{R^5}$ is phenyl which is optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl or *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; $\mathbf{R^1}$ is H or C_{1-6}alkyl; $\mathbf{R^2}$ is H, C_{1-6}alkyl (optionally substituted with one or more hydroxy, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, R^4, R^4C_{1-6}alkylsulphanyl, R^4C_{1-6}alkylsulphinyl or R^4C_{1-6}alkylsulphonyl), C_{1-6}alkoxy (optionally substituted with one or more halogen, C_{2-6}alkenyl, C_{2-6}alkynyl, R^4, R^4C_{2-6}alkenyl, R^4C_{2-6}alkynyl or Het), C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl,

N,N-(C_{1-6}alkyl)$_2$carbamoyl, R^4-, R^4S-, R^4C_{1-6}alkylsulphanyl, *N*-(R^4C_{1-6}alkyl)carbamoyl, *N*-(HetC_{1-6}alkyl)carbamoyl, C_{1-6}alkanoylamino, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl or C_{1-6}alkylsulphonyl; **R^4** is optionally substituted phenyl, or an optionally substituted 5 or 6 membered heteroaryl ring, said optional substituents on R^4 being chosen from one or more of C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl or *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, wherein two such adjacent groups may join to form a 6-membered saturated, partially saturated or unsaturated ring; **Het** is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms; and, **R^3** is H or C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof; for use as a medicament.

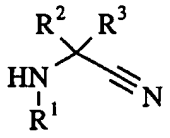
9. The use of a compound of formula (I) as claimed in claim 1 or 2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of a cysteine protease in a warm blooded animal.

10. The use of a compound of formula (I) as claimed in claim 1 or 2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease in a warm blooded animal.

11. A method of treating a Cathepsin L or Cathepsin S mediated disease state in mammals which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I) as claimed in claim 1 or 2, or a pharmaceutically acceptable salt thereof.

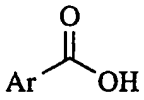
12. A process for preparing a compound of formula (I) as claimed in claim 1 or 2, the process comprising:

a) reacting an amine of formula **(II)**



(II)

with an acid of formula **(III)**

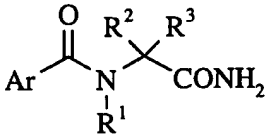


(III)

or a reactive derivative thereof;

or,

b) dehydrating an amide of formula **(IV)**

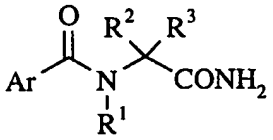


(IV)

under standard conditions;

wherein Ar, R^1, R^2 and R^3 are as defined in claim 1.

13. An intermediate compound of formula (IV):



(IV)

wherein Ar, R^1, R^2 and R^3 are as defined in claim 1.

INTERNATIONAL SEARCH REPORT

Int. Jonal Application No
PCT/GB 00/00539

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C255/29 C07C255/25 C07D307/54 C07D231/12 C07D295/08
C07C323/60 A61K31/275 A61K31/33 A61P19/00 C07D333/24
C07D249/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 061 836 A (IMPERIAL CHEMICAL INDUSTRIES PLC;UK) 6 October 1982 (1982-10-06) page 4 -page 9 page 13 -page 15 ---	1-6,8, 12,13
X	JP 60 169454 A (MITSUI TOATSU CHEMICALS, INC.;JAPAN) 2 September 1985 (1985-09-02) page 4 -page 5; tables page 6 ---	1-4,6,8, 12,13
X	US 4 447 446 A (KAY IAN T ET AL) 8 May 1984 (1984-05-08) column 3 -column 10; table 1 ---	1-6,8, 12,13
X	JP 60 255759 A (MITSUI TOATSU CHEMICALS, INC.;JAPAN) 17 December 1985 (1985-12-17) page 6 ---	1-5,8, 12,13

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 May 2000	23/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Pauwels, G

3

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte Jonal Application No
PCT/GB 00/00539

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	T UEDA ET AL: "Syntheses of 2-acylaminoacetamidine and 3-acylaminopropionamidine derivatives" CHEMICAL AND PHARMACEUTICAL BULLETIN,JP,TOKYO, vol. 12, no. 16, 1 January 1968 (1968-01-01), pages 2355-2361, XP002075777 ISSN: 0009-2363 page 2356; table I ---	1-6,8,12
X	B.F. CAIN: "2-Acyloxymethylbenzoic Acids. Novel amine protective functions providing amides with the lability of esters" JOURNAL OF ORGANIC CHEMISTRY, vol. 41, no. 11, 1976, pages 2029-2031, XP002136841 EASTON US page 2030, right-hand column, last line -page 2031, left-hand column, paragraph 1 ---	13
X	M. SEDLAK ET AL. : "Preparation, 1H and 13C NMR spectra of substituted 2-benzoylaminocarboxamides" COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, vol. 60, 1995, pages 150-160, XP002136842 PRAGUE CS page 151; figure III; table III ---	13
X	H. BRACHWITZ: "1,2,4-oxadiazole aus N-Acylaminonitrile" JOURNAL F. PRAKT. CHEMIE, vol. 314, no. 3, - 1972 pages 447-454, XP000908890 page 448; examples 4A-D ---	1-6,12
A	WO 98 23581 A (BASF AG ;MOELLER ACHIM (DE); LUBISCH WILFRIED (DE); TREIBER HANS J) 4 June 1998 (1998-06-04) -----	1-13

3

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/GB 00/00539

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0061836 A	06-10-1982	AT 24504 T	15-01-1987
		AU 600897 B	30-08-1990
		AU 5706986 A	06-11-1986
		AU 553145 B	03-07-1986
		AU 8114082 A	23-09-1982
		BR 8201503 A	01-02-1983
		CA 1208221 A	22-07-1986
		CA 1216303 C	06-01-1987
		DE 3274859 D	05-02-1987
		DK 121482 A	20-09-1982
		ES 510585 D	01-06-1983
		ES 8306482 A	01-09-1983
		GB 2095237 A,B	29-09-1982
		GR 76471 A	10-08-1984
		IE 52740 B	03-02-1988
		JP 57167978 A	16-10-1982
		NZ 199882 A	31-05-1985
		PH 18449 A	08-07-1985
		PH 19684 A	13-06-1986
		PT 74605 A,B	01-04-1982
		US 4432784 A	21-02-1984
		US 4506084 A	19-03-1985
		ZA 8201596 A	26-01-1983
JP 60169454 A	02-09-1985	NONE	
US 4447446 A	08-05-1984	AT 26701 T	15-05-1987
		AU 595526 B	05-04-1990
		AU 5732986 A	06-11-1986
		AU 551634 B	08-05-1986
		AU 8053082 A	09-09-1982
		BR 8201088 A	11-01-1983
		CA 1228366 A	20-10-1987
		CA 1233824 C	08-03-1988
		CY 1523 A	16-11-1990
		DE 3276110 D	27-05-1987
		DK 90182 A	05-09-1982
		EP 0059536 A	08-09-1982
		ES 510133 D	16-06-1983
		ES 8306996 A	01-10-1983
		ES 519845 D	16-03-1984
		ES 8403439 A	16-06-1984
		GB 2094786 A,B	22-09-1982
		GR 81364 A	11-12-1984
		HK 96490 A	30-11-1990
		HU 188779 B	28-05-1986
		IE 52718 B	03-02-1988
		IL 65079 A	31-03-1988
		JP 3043263 B	01-07-1991
		JP 57176938 A	30-10-1982
		NZ 199754 A	08-11-1985
		PH 20082 A	24-09-1986
		PH 21261 A	31-08-1987
		PH 21167 A	05-08-1987
		PH 21259 A	31-08-1987
		PT 74517 A,B	01-04-1982
		US 4579581 A	01-04-1986
		ZA 8201052 A	26-01-1983

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/GB 00/00539

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 60255759 A	17-12-1985	JP 1848793 C	07-06-1994
		JP 5059900 B	01-09-1993
WO 9823581 A	04-06-1998	DE 19648793 A	28-05-1998
		AU 5481498 A	22-06-1998
		BG 103433 A	29-02-2000
		CN 1238761 A	15-12-1999
		CZ 9901833 A	11-08-1999
		EP 0944584 A	29-09-1999
		HR 970637 A	31-10-1998
		NO 992492 A	25-05-1999
		PL 333505 A	20-12-1999